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September 28, 1956

Harris Isbell, M.D., Director
Addiction Research Center
National Institutes of Mental Health
U.S. Public Health Service Hospital
Box 2000
Lexington, Kentucky

Dear Dr. Isbell:

The information which I promised you is as follows:

Toxicity: In the mouse, by I.P. route, the LD_{50} is 390 mg/kg. In the dog, by I.V. route, it is 100 mg/kg. The minimum tranquilizing dose for the dog by the I.V. route is .05 mg/kg. The compound sometimes produces miosis, but often one can observe mydriasis. In the barbitalized dog, bradycardia is produced at a level of 0.1 mg/kg, I.V. This response is not blocked by prior atropinization or vagotomy. This bradycardia is also prominent in the intact, unanesthetized animal even at a lower dose. Hypothermia is prominent following 1 mg/kg, I.V., in the dog. The body temperature falls 4 to 7 degrees C. within 24 hours and gradually returns to normal over a several day period. At the dose level of 100 mg/kg severe diarrhea is produced in the dog. The nictitating membrane of the dog has a pure sympathetic innervation and is readily relaxed by this drug. This would seem to indicate that it reduces the normal central sympathetic outflow since the drug does not exhibit a characteristic adrenergic blocking action and ganglionic blockade is unlikely. As with all drugs in this series, ataxia is a prominent sign in the dog. With this particular material the effect begins to appear at about the minimum tranquilizing dose and is associated with respiratory depression. Both of these effects occur at dose levels below that required to produce bradycardia.

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The common carotid occlusion pressor response is dramatically reduced in the barbitalized dog within 30 minutes after the injection of small doses of this material. The pressor response elicited by central vagal stimulation may be greatly reduced or even reversed by small doses of the material. This drug apparently reduces the peripheral vascular resistance. This is manifested by decrease in minimum arterial blood pressure. A given dose of epinephrine at this point will produce a greater pressor response than it would before the drug was administered. The increased vascular response to epinephrine occurs in dogs with doses around 0.05 mg/kg. Inhibition of the C.C.O. pressor response likewise occurs at this dose. The dog's blood pressure is reduced about 30% by a dose of 0.1 mg/kg.

It seems strange to me that this material is not more antagonistic to LSD-25 than was indicated in the trials of the two given simultaneously. For this reason alone it would seem useful to study the drug further.

I'm looking forward to talking to you on the 17th.

Sincerely yours,

TSS [redacted] (23 September 1955)

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